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Immediate Postoperative 5-FU Does Not Decrease Colonic Anastomotic Strength

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Background and Objectives: The use of continuous infusion 5-Fluorouracil (5-FU) immediately after surgery may improve the adjuvant treatment of resected colon cancer and is the subject of a national phase III trial (Intergroup no. 0136). The aim was to determine the effect of continuous infusion 5-FU on the bursting pressure of a colon anastomosis.
Methods: Twenty Lewis rats weighing approximately 300 g were subject to sigmoid colectomy and single-layer anastomosis. Ten rats received 5-FU continuously at 600 mg/m^2 per day for 7 days; 10 rats served as controls. Ten days postoperatively, the rats were sacrificed and bursting pressure of the colon containing the anastomosis was determined.
Results: No anastomotic leaks or intra-abdominal abscesses were identified. Burst pressure of the colon in controls (124 ± 13 mm Hg; mean ± SEM) was not significantly different from those animals receiving 5-FU (115 ± 9, $P > 0.05$). The control rats gained weight (13 ± 7 g), which is significantly different from the rats receiving 5-FU (-19 ± 13, $P = 0.04$).
Conclusions: Continuous infusion 5-FU postoperatively results in weight loss, but does not affect anastomotic bursting strength in rats. This evidence supports the safety of continuous infusion 5-FU postoperatively in humans. *J. Surg. Oncol. 1998;69:125–127.*

KEY WORDS: chemotherapy; colorectal cancer; colonic anastomosis

INTRODUCTION

Colorectal cancer is the second leading cause of cancer death in the United States. The adjuvant treatment of colorectal cancer has been more successful than the treatment of measurable metastatic disease. Postoperative adjuvant chemotherapy has been shown to improve 5-year survival in stage III colon cancer [1]. Adjuvant chemoradiation improves survival in high-risk patients with rectal cancer [2]. In patients with colorectal cancer, treatment is most effective when the tumor burden is below current means to detect it [3].

Once colon cancer is diagnosed, tumor burden is lowest and cell replication most rapid in the immediate postoperative period. It is logical that adjuvant chemotherapy would have its greatest chance of efficacy at this time [4]. Thus, interest has developed in giving adjuvant chemotherapy in the time immediately following surgery. Past animal studies have shown that systemic 5-FU given as a bolus leads to increased anastomotic complications. However, continuous infusion 5-FU was shown to be safe in a small Australian trial [5] and has become the subject of a national multigroup trial sponsored by the NCI (Intergroup Study no. 0136). Early results for this trial show no increase in complication in those patients receiving postoperative 5-FU [6].

However, there continues to be considerable uncertainty among surgeons as to the influence of early postoperative continuous infusion 5-FU on the healing of colorectal anastomosis. The effect of continuous infusion 5-FU on anastomotic strength has never been tested. The aim of this study was to evaluate whether 5-FU given as a continuous infusion for 1 week immediately postoperatively weakened the colonic anastomosis.

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MATERIALS AND METHODS

Preparation of Rats

Surgical procedures, postoperative care, and euthanasia of the rats were performed according to the University of Missouri guidelines after approval by the Animal Care and Use Committee of the University of Missouri, Columbia. Twenty Lewis rats weighing approximately 300 g underwent mechanical cleansing of the bowel with clear liquids and magnesium citrate given 24 hr preoperatively. Under ether anesthesia, the rats were subjected to sigmoid colectomy and single-layer anastomosis with eight interrupted 5-0 polygalactic sutures. The anastomosis was constructed 2 cm above the peritoneal reflection. The abdominal fascia was closed with 4-0 polygalactic sutures in a running fashion and the skin closed with staples. An incision was then made in the ventral neck, just to one side of the midline. A subcutaneous tunnel was made to the mid-scapular area and two Alzet (Alza, Palo Alto, CA) 2-ml osmotic pumps were placed. A Y-shaped catheter connected the osmotic pumps to a single catheter that was placed in the external jugular vein and threaded to the level of the superior vena cava. The skin was closed with staples. All rats receive penicillin G (0.15 mg/Kg) and gentamicin (1 mg/Kg) 1 hr preoperatively and 8 hr postoperatively.

Chemotherapy Delivery

The rats were randomized to receive 5-FU 600 mg/m^2/day or an equal volume of saline as a control. Each Alzet osmotic pump (model 2ML1) delivers 10 μl/hr for 7 days. The osmotic pumps were filled completely with the saline or saline + 5-FU solution to obtain the appropriate dosage of drug. Postoperatively, the rats were given water for 24 hr and then allowed regular rat chow.

Colonic Strength Evaluation

On postoperative day 10, the rats underwent euthanasia in a CO_2 chamber. The weight was recorded and a blood sample taken to measure the leukocyte count. A 5-cm section of the colon containing the anastomosis was harvested. The colonic segment was closed around a catheter at both ends. The distal catheter was connected to an infusion pump and the proximal catheter to a manometer. The colon was submerged in water. Air was then infused at a constant rate of 5 ml/min. The bursting pressure was defined as the pressure where air could be seen escaping from the colonic segment and bubbling up in the bath containing the colon. The site and pressure at which rupture occurred was noted.

Statistics

Continuous normally distributed data is reported as mean ± SEM. Groups were compared using a two-tailed Student's *t*-test for unpaired data. Categorical data was evaluated using Fischer's exact test. Differences were considered significant at $P < 0.05$.

RESULTS

All rats tolerated food, appeared well, and survived 10 days. At autopsy, no anastomotic leaks or intra-abdominal abscesses were identified. Adhesions were present in both groups of rats, and were of similar density and number. Burst pressure of the colon in controls (124 ± 13 mm Hg; mean ± SEM) was not significantly different from those animals receiving 5-FU (115 ± 9). The site of rupture was the anastomosis in all rats, except one control and two 5-FU rats in which rupture occurred at a colonic site remote from the anastomosis. The control rats gained weight (13 ± 7 g), while the rats receiving 5-FU lost weight (−19 ± 13, $P = 0.04$). The leukocyte count at the time of sacrifice was similar in the 5-FU (4,200 ± 500/mm^3) and control (4,400 ± 400/mm^3) animals.

DISCUSSION

Surgeons are reluctant to prescribe 5-FU in the immediate postoperative period. This is primarily due to the belief that the 5-FU will increase the anastomotic leak rate. This can result in the need for reoperation, creation of a colostomy, and need for a future takedown, or even death. It is estimated that one out of three postoperative deaths after colonic surgery is due to a leaking anastomosis [7].

The dangers of postoperative 5-FU have been well documented. Several animal studies have documented a weaker anastomosis and increased risk of anastomotic rupture when systemic 5-FU is given as a bolus immediately postoperatively [8,9]. Immediate intraperitoneal 5-FU also increases the risk of anastomotic dehiscence [10]. Early postoperative use of 5-FU by the intraportal route appears to be safe in the adjuvant treatment of colon cancer [11]. This is attributed to decreased systemic 5-FU due to metabolism of the 5-FU at its first pass through the liver.

In recent years, it has been documented that continuous infusion 5-FU allows the use of greater daily dosages and appears safer than bolus 5-FU [12]. This has encouraged surgeons to revisit the idea of giving 5-FU in the immediate postoperative period. Continuous infusion avoids the high-peak serum levels of 5-FU seen with bolus dosing and may be an effective adjuvant for colon cancer without increasing the anastomotic leak rate. The main finding in this study is that 5-FU given as a continuous infusion at 600 mg/m^2 for 1 week immediately postoperatively does not decrease anastomotic strength.

There are some deficiencies to this study. First, the anastomotic strength was only tested at 10 days. For more confidence it should also be tested earlier in the postoperative period. Second, the rat 5-FU metabolism

may be more efficient than that seen in humans. Thus, species differences in the effect of 5-FU on the anastomosis may be present. Finally, these were not tumor-bearing rats. Thus, any influence of neoplasm on the anastomosis would not be evident in this study.

There have been some studies directly evaluating the strength of colonic anastomoses under different conditions. Christensen et al. [13] shows that anastomotic strength gradually increases postoperatively, reaching a plateau at 10 days. Recent studies show that corticosteroids reduce the strength of anastomotic healing in the postoperative period [14,15]. Both preoperative [16] and intraoperative [17] external beam radiation therapy decrease anastomotic strength in the postoperative period. However, anastomotic complications do not appear to be more common in man following preoperative radiation [18,19].

There is recent enthusiasm for the use of preoperative chemoradiation in rectal cancer [20,21]. This may downstage tumors and allow sphincter-sparing procedures. Preoperative 5-FU can be given without decreasing anastomotic strength postoperatively [22]. The influence of preoperative chemoradiation on anastomotic strength has not been studied. Should perioperative chemotherapy provide a survival benefit in colon cancer, it would be logical to evaluate its use in rectal cancer. Thus, the anastomotic strength of a rectal anastomosis subject to preoperative chemoradiation and immediate postoperative chemotherapy needs to be evaluated.

In summary, this study documents that continuous infusion 5-FU at 600 mg/m^2 for 7 days does not result in a weaker colonic anastomosis in the rat 10 days postoperatively. This occurs despite a loss in weight in rats receiving 5-FU. In addition, leukocyte counts do not change significantly. These results are reassuring and should encourage surgeons to support the current intergroup study evaluating immediate postoperative 5-FU after curative resection for patients with colon cancer.

REFERENCES

1. Moertel CG, Fleming TR, Macdonald JS, et al.: Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med 1990;322:352–358.
2. Krook JE, Moertel CG, Gunderson LL, et al.: Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med 1991;324:709–715.
3. Nordic Gastrointestinal Tumor Adjuvant Therapy Group: Expectant or primary chemotherapy in patients with advanced asymptomatic colorectal cancer: a randomized trial. J Clin Oncol 1992; 10:904–911.
4. DeVita VT: The relationship between tumor mass and resistance to treatment of cancer. Cancer 1983;51:1209.
5. Gray B, deZwart J, Fisher R, et al.: The Australian and New Zealand trial of adjuvant chemotherapy in colon cancer. In Salmon SE (ed): Adjuvant therapy of cancer V. Orlando, FL: Grune & Stratton; 1987:537–546.
6. Kemeny MM, Ibrahim J, Benson AB: Postoperative complications of continuous infusion 5-FU following curative resection of colon cancer: ECOG 1292. Proc ASCO 1997;16:261a.
7. Debas HT, Thompson FB: A critical review of colectomy with anastomosis. Surg Gynecol Obstet 1972;135:747–752.
8. Goldman LI, Lowe S, al-Saleem T: Effect of fluorouracil on intestinal anastomoses in the rat. Arch Surg 1969;98:303–304.
9. Morris T: Retardation of healing of large-bowel anastomoses by 5-fluorouracil. Aust NZ J Surg 1979;49:743–745.
10. Weiber S, Graf W, Gilmelius B, et al.: Experimental colonic healing in relation to timing of 5-fluorouracil therapy. Br J Surg 1994; 88:1677–1680.
11. Wolmark N, Rockette H, Wickerham DL, et al.: Adjuvant therapy of Dukes A, B, and C adenocarcinoma of the colon with portal-vein fluorouracil hepatic infusion: preliminary results of National Surgical Adjuvant Breast and Bowel Project C-02. J Clin Oncol 1990;8:1466–1475.
12. Lokich JJ, Ahlgren JD, Gullo JJ, et al.: A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a Mid-Atlantic Oncology Program Study. J Clin Oncology 1989;7:425–432.
13. Christensen H, Langfert S, Laurberg S: Bursting strength of experimental colonic anastomosis. Eur Surg Res 1993;25:38–45.
14. Furst MB, Stromberg BV, Blotchford GJ, et al.: Colonic anastomoses: bursting strength after corticosteroid treatment. Dis Colon Rectum 1994;37:12–15.
15. DelRio JV, Beck DE, Opelka FG: Chronic perioperative steroids and colonic anastomotic healing in rats. J Surg Res 1996;66:138–142.
16. Milson JW, Senagore A, Walshaw RK, et al.: Preoperative radiation therapy produces an early and persistent reduction in colorectal anastomotic blood flow. J Surg Res 1992;53:464–469.
17. Seifert WF, Wobbes T, Hoogenhout J, et al.: Intraoperative irradiation delays anastomotic repair in rat colon. Am J Surg 1995; 170:256–261.
18. Pahlmon L, Glimelius B: Preoperative and postoperative radiotherapy and rectal cancer. World J Surg 1992;16:858–865.
19. Stockholm Colorectal Cancer Study Group: Randomized study on preoperative radiotherapy in rectal carcinoma. Ann Surg Onc 1996;3:423–430.
20. Minsky B, Cohen A, Enker W, et al.: Preoperative 5-fluorouracil, low-dose leucovorin, and concurrent radiation therapy for rectal cancer. Cancer 1994;73:273–278.
21. Rich TA, Skibber JM, Ajani JA, et al.: Preoperative infusional chemoradiation therapy for Stage T3 rectal cancer. Int J Rad Onc Biol Phys 1995;32:1025–1029.
22. Hananel N, Gordon PH: Effect of 5-fluorouracil and leucovorin on the integrity of colonic anastomoses in the rat. Dis Colon Rectum 1995;38:886–890.